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The Relationships Between Time in Range, Hyperglycemia Metrics, and HbA1c

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Abstract

Background: As the use of continuous glucose monitoring (CGM) increases, there is a need to better understand key metrics of time in range 70-180 mg/dL ($TIR^{70\text{-}180}$) and hyperglycemia and how they relate to hemoglobin A1c (A1C).

Methods: Analyses were conducted utilizing datasets from four randomized trials encompassing 545 adults with type 1 diabetes (T1D) who had central-laboratory measurements of A1C. CGM metrics were calculated and compared with each other and A1C cross-sectionally and longitudinally.

Results: Correlations among CGM metrics ($TIR^{70\text{-}180}$, time >180 mg/dL, time >250 mg/dL, mean glucose, area under the curve above 180 mg/dL, high blood glucose index, and time in range 70-140 mg/dL) were typically 0.90 or greater. Correlations of each metric with A1C were lower (absolute values 0.66-0.71 at baseline and 0.73-0.78 at month 6). For a given $TIR^{70\text{-}180}$ percentage, there was a wide range of possible A1C levels that could be associated with that $TIR^{70\text{-}180}$ level. On average, a $TIR^{70\text{-}180}$ of 70% and 50% corresponded with an A1C of approximately 7% and 8%, respectively. There also was considerable spread of change in A1C for a given change in $TIR^{70\text{-}180}$, and vice versa. An increase in $TIR^{70\text{-}180}$ of 10% (2.4 hours per day) corresponded to a decrease in A1C of 0.6%, on average.

Conclusions: In T1D, CGM measures reflecting hyperglycemia (including TIR and mean glucose) are highly correlated with each other but only moderately correlated with A1C. For a given TIR or change in TIR there is a wide range of possible corresponding A1C values.

Keywords

type 1 diabetes, continuous glucose monitoring, glucose time in range

In recent years, advances in continuous glucose monitoring (CGM) technology have led to a substantial increase in CGM use. At the same time, limitations of hemoglobin A1c (A1C), which has been the gold standard for assessing both individual, group, and population glycemic control, have received increasing attention.[1] Numerous studies have shown that there are a wide range of possible mean glucose levels for a given A1C level,[1-5] meaning that for some patients, A1C may not be a reliable indicator of glucose control. In addition, A1C primarily reflects hyperglycemia and does not provide information about hypoglycemia, glycemic variability, or the daily pattern of glucose concentrations.

As CGM use continues to increase, there is the need to better understand CGM metrics and patterns, and their key role in diabetes management. Recently, several organizations have published consensus statements on specific CGM metrics to use for assessing hyperglycemia, hypoglycemia, and glycemic variability.[6,7] Time >180 mg/dL ($T>^{180}$) and time >250 mg/dL ($T>^{250}$) are the two consensus hyperglycemia metrics. Other common metrics which are highly correlated with hyperglycemia and thus largely measures of hyperglycemia are time in range of 70-180 mg/dL ($TIR^{70\text{-}180}$) and mean glucose concentration. In this

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Table 1. Descriptions of the Four Studies.

	JDRF CGM RCT[a]	DIAMOND (T1D)	REPLACE-BG	HypoDE
Time period of study	February 2007-June 2009	October 2014-May 2016	May 2015-September 2016	March 2016-July 2017
CGM(s)	Dexcom Seven, MiniMed Paradigm, Abbott Freestyle Navigator	Dexcom G4 with software 505	Dexcom G4 with software 505	Dexcom G5
Method for A1C measurement	A1C measured with NGSP-certified method (Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer), performed at University of Minnesota	A1C measured with NGSP-certified method (G8 Tosoh Biosciences), performed at Northwest Lipid Research Laboratories, University of Washington, Seattle	A1C measured with NGSP-certified method (G8 Tosoh Biosciences), performed at Northwest Lipid Research Laboratories, University of Washington, Seattle	A1C measured with NGSP-certified method (G8 Tosoh Biosciences), performed at MLM Medical Labs, Moenchengladbach, Germany
A1C eligibility range	≤10.0%	7.5%-9.9%	≤9.0%	≤9.0%
Insulin delivery	Pump and MDI users (predominately pump)	100% MDI	100% pump users	100% MDI
Number of participants included in the analyses	93	99	212	141
Age (years)				
Mean ± SD	38 ± 13	46 ± 14	45 ± 14	46 ± 11
[Range]	[18 to 73]	[26 to 72]	[20 to 78]	[20 to 69]
Female %	52 (56%)	43 (43%)	107 (50%)	56 (40%)
White race %	90 (97%)	86 (88%)	195 (92%)	n/a
Diabetes duration (years)				
Median (IQR)	20 (14-31)	19 (9-31)	23 (15-32)	21 (9-31)
[Range]	[2 to 63]	[2 to 57]	[2 to 64]	[2 to 54]
A1C (%)—baseline				
Mean ± SD	7.2 ± 0.8	8.6 ± 0.7	7.1 ± 0.6	7.5 ± 1.0
[Range]	[4.7 to 9.2]	[7.5 to 9.9]	[5.2 to 8.7]	[4.9 to 10.0]
A1C (%)—6 months				
Mean ± SD	6.8 ± 0.6	7.6 ± 0.8	7.0 ± 0.7	7.3 ± 0.9
[Range]	[5.0 to 8.9]	[6.0 to 10.1]	[5.2 to 8.8]	[5.3 to 9.7]
A1C—change from baseline (%)				
Mean ± SD	−0.4 ± 0.5	−1.0 ± 0.8	0.0 ± 0.5	−0.2 ± 0.5
[Range]	[−2.0 to +0.9]	[−3.0 to +0.7]	[−1.4 to +1.4]	[−1.8 to +1.5]

[a]Includes both the A1C ≥7.0% and A1C <7.0% cohorts.

article, we evaluate multiple aspects of these common CGM-measured hyperglycemia metrics and their relationship to A1C to facilitate the effective use of CGM to optimize diabetes management.

Methods

Analyses were conducted utilizing datasets from 4 randomized trials that included participants ≥18 years old with type 1 diabetes. Each study assessed CGM as an intervention over a 6-month period and had central-laboratory measurements of A1C at baseline and 6 months. One clinical trial (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Randomized Clinical Trial [JDRF CGM RCT]) included the 3 commercially available CGM systems at the time of the study (Dexcom™ SEVEN® Dexcom, Inc, San Diego, CA; MiniMed Paradigm® REAL-Time Insulin Pump and Continuous Glucose Monitoring System, Medtronic MiniMed, Inc, Northridge, CA; FreeStyle Navigator™, Abbott Diabetes Care, Inc, Alameda, CA),[8,9] while the other 3 (DIAMOND, REPLACE-BG, and HypoDE) utilized a Dexcom G4 sensor with 505 software.[10-12] Participants included in the analyses were in a treatment arm using CGM as an intervention and had a minimum of 336 hours (14 days) of CGM values in month 6. For analyses reporting baseline data or assessing change from baseline, a minimum of 240 hours (10 days) of masked baseline CGM data were required. Table 1 provides details of the 4 studies.

Statistical Methods

The main CGM metrics included in the analyses were $TIR^{70\text{-}180}$, $T{>}^{180}$, $T{>}^{250}$, and mean glucose. In addition, the following CGM metrics also were tabulated and included in some analyses: area under the curve above 180 mg/dL (AUC$>^{180}$), high blood glucose index (HBGI, which provides an increasing influence to values based on the extent of hyperglycemia),[13] time $<$ 70 mg/dL (T$<^{70}$), time $<$54 mg/dL (T$<^{54}$), and time in range 70-140 mg/dL (TIR$^{70\text{-}140}$).

Mean ± SD or median (interquartile range [IQR]) are reported as appropriate for the distribution of data. Spearman partial correlations were calculated, adjusting for study, among A1C and CGM metrics at baseline, at month 6, and change from baseline to month 6. Least squares regression models were used to assess the relationships between A1C and TIR$^{70\text{-}180}$, TIR$^{70\text{-}140}$, and T$>^{180}$ at baseline and at month 6, and to assess the relationship between change in A1C and change in these metrics from baseline to month 6. Analyses also were conducted to assess the relationship between changes in above metrics according to baseline A1C levels.

Analyses were repeated using data from only the 3 studies using the Dexcom G4 (with 505 software) sensor with similar results (results not shown). Analyses also were replicated by creating a dataset in which every third glucose value was retained to mirror a sensor with glucose measurements every 15 minutes; the results were virtually identical (results not shown).

Results

The cross-sectional analyses at 6 months included data from 545 study participants. Mean age was 44 ± 13 years (range 18 to 78 years), 47% were female, and 92% were white. Median diabetes duration was 21 years (IQR 12 to 31, range 2 to 64 years). Mean A1C was 7.5 ± 1.0% (range 4.7% to 10.0%) at baseline and 7.2 ± 0.8% (range 5.0% to 10.1%) at 6 months. Participant characteristics in each of the 4 studies are provided in Table 1. The distributions of their CGM metrics at baseline and month 6 are shown in Table 2.

As can be seen in Table 3 and Figures S1, and S2, correlations among the CGM metrics were typically 0.9 or higher at baseline and 6 months. All 7 CGM metrics had a lower correlation with A1C than with each other (absolute value 0.66-0.71 at baseline and 0.73-0.78 at month 6). Despite the moderate correlation between TIR$^{70\text{-}180}$ and A1C (−0.67 at baseline and −0.73 at month 6), for a given TIR$^{70\text{-}180}$ level, there was a wide range of possible A1C levels that could be associated with that TIR$^{70\text{-}180}$ (Figure 1 for month 6 and Figure S3 for baseline). Likewise there was a wide range of possible TIR$^{70\text{-}180}$ levels associated with a given A1C level (Figure S4). This is evident in the 95% confidence limits for a predicted A1C for a specified TIR$^{70\text{-}180}$ (Table 4a) and the confidence limits for TIR$^{70\text{-}180}$ for a specified A1C (Table 4b). Note that the equation to predict TIR from A1C is not simply a rearrangement of the equation for predicting A1C from TIR. A similar degree of dispersion was seen for mean glucose, T$>^{180}$, T$>^{250}$, and TIR$^{70\text{-}140}$ versus A1C (Figures 1, S3, and S5).

Correlations (absolute value) of change from baseline among CGM metrics ranged from 0.70 (TIR$^{70\text{-}140}$ versus T$>^{250}$) to 0.99 (AUC$>^{180}$ versus HBGI) whereas correlations of change in CGM metrics versus change in A1C ranged from 0.47 to 0.52 (Table 3). Figure 2 and Table 5a show the change in A1C for a specified change in TIR$^{70\text{-}180}$ from baseline to 6 months. As in the cross-sectional analysis, there was considerable spread of A1C change values for a specified TIR$^{70\text{-}180}$ change value. Although, the slope for change in A1C versus change in TIR$^{70\text{-}180}$ was not significantly influenced by baseline A1C level (P = .22 for interaction term), the magnitude of change in A1C was greater the higher the baseline A1C (Figure 2, Table 5a). Results were similar comparing change in T$>^{180}$ and change in A1C (Figure 3, Table 5a). Change in TIR$^{70\text{-}180}$ for a given change in A1C is shown in Table 5b, and change in A1C for a given change in TIR$^{70\text{-}140}$ is shown in Figure S6.

Discussion

The analyses of this large type 1 diabetes CGM dataset confirm that CGM metrics that are measures of or largely reflect hyperglycemia, including TIR and mean glucose, are highly correlated with each other, suggesting that there may not be a meaningful statistical advantage to AUC$>^{180}$ and HBGI over simpler percentage of time metrics, as noted by Rodbard.[14]

The correlation of the CGM metrics with A1C is only moderate. In relating TIR$^{70\text{-}180}$ to A1C, results were slightly different for masked baseline data at the time of study entry versus the data during month 6, with estimated mean A1C tending to be slightly lower for a given TIR$^{70\text{-}180}$ or T$>^{180}$ at month 6 than at baseline . This might be reflecting a shift in the mean values due to use of CGM in diabetes management for 6 months and therefore also a shift in the regression lines; at baseline, most of the participants were not using CGM for diabetes management. For a specified TIR$^{70\text{-}180}$, there was a wide range of possible A1C levels which is apparent when observing a graph of TIR$^{70\text{-}180}$ versus A1C. This finding also was present for the other measures of hyperglycemia and is essentially identical to observations from numerous researchers with respect to the mean glucose versus A1C relationship.[1,5] Although TIR$^{70\text{-}180}$ of 50% on average is associated with an A1C level of about 8%, the actual A1C could be substantially lower (eg, 6.6%) or higher (eg, 9.2%). Likewise, on average, a TIR$^{70\text{-}180}$ of 30% is associated with an A1C of about 8.7% and a TIR$^{70\text{-}180}$ of 70% is associated with an A1C of about 7.0%. Assuming there is not measurement error, discordance when present may reflect interindividual differences in red blood cell lifespan or other factors that influence A1C levels unrelated to the degree of glycemia.[3,4] Several studies have demonstrated that an individual's mean glucose-A1C relationship tends to be reasonably constant over time and presumably the TIR-A1C relationship would be as well.[15-17]

Table 2. CGM Metrics at Baseline and 6 Months According to Study.

	All	JDRF	Diamond T1D	Replace-BG	HypoDE
N[a]	545	93	99	212	141
CGM at baseline					
N	455	4	98	212	141
Amount of CGM data (hours)					
Mean ± SD	558 ± 141	306 ± 45	324 ± 48	614 ± 76	642 ± 43
Median (IQR)	633 (473-651)	290 (274-337)	315 (305-320)	641 (620-651)	642 (615-661)
[Range]	[248-795]	[273 to 370]	[248 to 477]	[270 to 684]	[546 to 795]
$TIR^{70\text{-}180}$ (%)					
Mean ± SD	58 ± 15	56 ± 20	46 ± 12	64 ± 13	59 ± 14
Median (IQR)	58 (48-68)	61 (40-72)	47 (37-54)	64 (55-72)	58 (48-67)
[Range]	[13 to 97]	[30 to 74]	[13 to 80]	[16 to 97]	[23 to 97]
$TIR^{70\text{-}140}$ (%)					
Mean ± SD	37 ± 13	33 ± 15	28 ± 10	40 ± 13	38 ± 14
Median (IQR)	36 (28-44)	36 (21-45)	28 (22-34)	39 (31-47)	37 (29-46)
Range	[2 to 94]	[13 to 47]	[5 to 57]	[2 to 94]	[7 to 94]
$T{>}^{180}$ (%)					
Mean ± SD	37 ± 16	43 ± 21	49 ± 14	33 ± 13	34 ± 17
Median (IQR)	36 (26, 48)	38 (26, 59)	48 (38, 56)	32 (24, 42)	34 (22, 46)
[Range]	[0 to 85]	[26 to 69]	[12 to 85]	[1 to 84]	[0 to 76]
$T{>}^{250}$ (%)					
Mean ± SD	13 ± 10	14 ± 12	22 ± 11	9 ± 7	12 ± 9
Median (IQR)	10 (5, 18)	11 (5, 24)	21 (13, 28)	7 (4, 13)	8 (5, 17)
[Range]	[0 to 51]	[4 to 31]	[3 to 51]	[0 to 33]	[0 to 40]
Mean glucose (mg/dL)					
Mean ± SD	166 ± 27	177 ± 30	186 ± 26	160 ± 21	160 ± 28
Median (IQR)	164 (148, 182)	172 (153, 201)	182 (165, 201)	159 (148, 174)	156 (141, 181)
[Range]	[89 to 250]	[149 to 216]	[121 to 250]	[99 to 223]	[89 to 240]
$AUC{>}^{180}$ mg/dL					
Mean ± SD	23 ± 15	26 ± 18	37 ± 17	18 ± 11	21 ± 15
Median (IQR)	19 (12-31)	22 (12-39)	34 (24-46)	16 (10-24)	17 (10-29)
[Range]	[0 to 84]	[10 to 48]	[6 to 84]	[0 to 55]	[0 to 67]
HBGI					
Mean ± SD	8.7 ± 4.4	9.9 ± 5.1	12.5 ± 4.6	7.4 ± 3.3	8.1 ± 4.3
Median (IQR)	8.1 (5.7, 11.4)	8.9 (5.8, 13.9)	11.9 (9.2, 14.8)	6.9 (5.1, 9.6)	7.4 (4.8, 10.9)
[Range]	[0.2 to 24.1]	[5.3 to 16.5]	[3.4 to 24.1]	[0.4 to 17.6]	[0.2 to 21.2]
$T{<}^{70}$ (%)					
Mean ± SD	5.0 ± 4.5	1.1 ± 1.0	5.4 ± 4.0	3.5 ± 2.5	7.2 ± 6.0
Median (IQR)	3.7 (2.1-6.6)	0.7 (0.5-1.6)	4.4 (2.3-7.4)	3.0 (1.7-4.6)	5.7 (2.9-9.8)
Range	[0.0 to 34.7]	[0.2 to 2.5]	[0.0 to 20.1]	[0.0 to 13.1]	[0.0 to 34.7]
$T{<}^{54}$ (%)					
Mean ± SD	1.7 ± 2.3	0.2 ± 0.2	2.1 ± 2.2	0.8 ± 0.8	2.8 ± 3.2
Median (IQR)	0.8 (0.4, 2.3)	0.2 (0.0, 0.3)	1.2 (0.6, 3.0)	0.6 (0.2, 1.0)	1.9 (0.7, 3.7)
Range	[0.0 to 18.1]	[0.0 to 0.4]	[0.0 to 9.3]	[0.0 to 5.2]	[0.0 to 18.1]
CGM in Month 6					
N	545	93	99	212	141
Amount of CGM data (hours)					
Mean ± SD	607 ± 73	510 ± 81	607 ± 65	620 ± 50	652 ± 36
Median (IQR)	635 (589, 653)	526 (454, 576)	634 (579, 649)	637 (612, 651)	657 (639, 671)
[Range]	[340 to 803]	[340 to 653]	[345 to 661]	[371 to 663]	[508 to 803]
$TIR^{70\text{-}180}$ (%)					
Mean ± SD	61 ± 15	70 ± 13	51 ± 14	64 ± 13	58 ± 15
Median (IQR)	62 (51, 72)	71 (64, 80)	52 (41, 59)	64 (56, 73)	58 (47, 68)
[Range]	[11 to 99]	[29 to 94]	[11 to 87]	[19 to 97]	[19 to 99]

(continued)

Table 2. (continued)

	All	JDRF	Diamond T1D	Replace-BG	HypoDE
$TIR^{70\text{-}140}$ (%)					
Mean ± SD	39 ± 14	47 ± 13	30 ± 11	41 ± 13	36 ± 15
Median (IQR)	38 (29-47)	47 (40-54)	31 (22-38)	39 (32-49)	35 (26-44)
Range	[4 to 96]	[15 to 86]	[5 to 72]	[4 to 96]	[5 to 88]
$T>^{180}$ (%)					
Mean ± SD	35 ± 16	25 ± 13	46 ± 15	32 ± 14	37 ± 17
Median (IQR)	34 (23, 45)	24 (16, 33)	44 (35, 56)	32 (22, 42)	36 (26, 51)
[Range]	[0 to 89]	[1 to 69]	[3 to 89]	[0 to 81]	[1 to 81]
$T>^{250}$ (%)					
Mean ± SD	11 ± 10	6 ± 6	18 ± 12	9 ± 7	12 ± 10
Median (IQR)	8 (4, 16)	4 (2, 7)	17 (9, 24)	7 (4, 13)	10 (4, 17)
[Range]	[0 to 68]	[0 to 33]	[0 to 68]	[0 to 33]	[0 to 48]
Mean glucose (mg/dL)					
Mean ± SD	163 ± 27	148 ± 21	181 ± 28	158 ± 22	166 ± 29
Median (IQR)	160 (144, 179)	145 (137, 156)	177 (163, 197)	158 (143, 174)	163 (147, 187)
[Range]	[93 to 278]	[109 to 218]	[111 to 278]	[93 to 219]	[101 to 255]
$AUC>^{180}$ (mg/dL)					
Mean ± SD	20 ± 15	12 ± 10	31 ± 18	17 ± 11	22 ± 16
Median (IQR)	17 (9, 28)	10 (6, 14)	29 (18, 40)	15 (9, 23)	19 (11, 29)
[Range]	[0 to 102]	[0 to 52]	[1 to 102]	[0 to 51]	[0 to 82]
HBGI					
Mean ± SD	8.0 ± 4.4	5.7 ± 3.1	11.3 ± 5.0	7.2 ± 3.3	8.7 ± 4.6
Median (IQR)	7.3 (4.9, 10.4)	5.0 (3.7, 6.8)	10.7 (7.5, 13.9)	7.0 (4.7, 9.2)	8.1 (5.4, 11.3)
[Range]	[0.1 to 29.6]	[0.7 to 17.3]	[1.1 to 29.6]	[0.1 to 17.0]	[0.7 to 24.7]
$T<^{70}$ (%)					
Mean ± SD	4.2 ± 3.9	4.2 ± 3.6	3.7 ± 3.2	3.9 ± 3.2	5.0 ± 5.1
Median (IQR)	3.1 (1.5, 5.7)	3.3 (1.8, 5.7)	2.7 (1.6, 4.7)	3.1 (1.6, 5.5)	3.4 (1.1, 6.5)
Range	[0.0 to 21.6]	[0.2 to 20.6]	[0.1 to 16.7]	[0.0 to 17.0]	[0.0 to 21.6]
$T<^{54}$ (%)					
Mean ± SD	1.2 ± 1.8	1.0 ± 1.6	1.1 ± 1.6	1.0 ± 1.1	1.9 ± 2.7
Median (IQR)	0.6 (0.2, 1.5)	0.4 (0.1, 1.3)	0.5 (0.2, 1.3)	0.6 (0.2, 1.3)	0.7 (0.1, 2.3)
Range	[0.0 to 12.3]	[0.0 to 11.3]	[0.0 to 10.2]	[0.0 to 7.1]	[0.0 to 12.3]

[a]Total number of participants included in analyses (with nonmissing CGM data at month 6).

Table 3. Spearman Partial Correlation Among A1C and Selected CGM Metrics.[a]

	$TIR^{70\text{-}180}$	$TIR^{70\text{-}140}$	$T>^{180}$	$T>^{250}$	Mean glucose	$AUC>^{180}$	HBGI	A1C
Baseline data								
$TIR^{70\text{-}180}$	+1.00	+0.94	−0.96	−0.94	−0.92	−0.96	−0.96	−0.67
$TIR^{70\text{-}140}$	+0.94	+1.00	−0.97	−0.86	−0.95	−0.90	−0.94	−0.69
$T>^{180}$	−0.96	−0.97	+1.00	+0.92	+0.98	+0.95	+0.98	+0.70
$T>^{250}$	−0.94	−0.86	+0.92	+1.00	+0.92	+0.99	+0.97	+0.66
Mean glucose	−0.92	−0.95	+0.98	+0.92	+1.00	+0.95	+0.98	+0.71
$AUC>^{180}$	−0.96	−0.90	+0.95	+0.99	+0.95	+1.00	+0.99	+0.69
HBGI	−0.96	−0.94	+0.98	+0.97	+0.98	+0.99	+1.00	+0.71
A1C	−0.67	−0.69	+0.70	+0.66	+0.71	+0.69	+0.71	+1.00
Month 6 data								
$TIR^{70\text{-}180}$	+1.00	+0.95	−0.96	−0.95	−0.92	−0.96	−0.96	−0.73
$TIR^{70\text{-}140}$	+0.95	+1.00	−0.97	−0.88	−0.96	−0.92	−0.95	−0.75
$T>^{180}$	−0.96	−0.97	+1.00	+0.93	+0.98	+0.96	+0.98	+0.77
$T>^{250}$	−0.95	−0.88	+0.93	+1.00	+0.92	+0.99	+0.97	+0.73

(continued)

Table 3. (continued)

	TIR^{70-180}	TIR^{70-140}	$T>^{180}$	$T>^{250}$	Mean glucose	$AUC>^{180}$	HBGI	A1C
Mean glucose	−0.92	−0.96	+0.98	+0.92	+1.00	+0.95	+0.98	+0.78
$AUC>^{180}$	−0.96	−0.92	+0.96	+0.99	+0.95	+1.00	+0.99	+0.75
HBGI	−0.96	−0.95	+0.98	+0.97	+0.98	+0.99	+1.00	+0.77
A1C	−0.73	−0.75	+0.77	+0.73	+0.78	+0.75	+0.77	+1.00
Change from baseline to month 6								
TIR^{70-180}	+1.00	−0.90	−0.94	−0.80	−0.85	−0.85	−0.88	−0.47
TIR^{70-140}	+0.90	+1.00	−0.91	−0.70	−0.87	−0.76	−0.84	−0.49
$T>^{180}$	−0.94	−0.91	+1.00	+0.82	+0.95	+0.88	+0.94	+0.51
$T>^{250}$	−0.80	−0.70	+0.82	+1.00	+0.88	+0.97	+0.95	+0.45
Mean glucose	−0.85	−0.87	+0.95	+0.88	+1.00	+0.93	+0.97	+0.52
$AUC>^{180}$	−0.85	−0.76	+0.88	+0.97	+0.93	+1.00	+0.99	+0.48
HBGI	−0.88	−0.84	+0.94	+0.95	+0.97	+0.99	+1.00	+0.50
A1C	−0.47	−0.49	+0.51	+0.45	+0.52	+0.48	+0.50	+1.00

[a]The Spearman partial correlation is adjusted for studies.

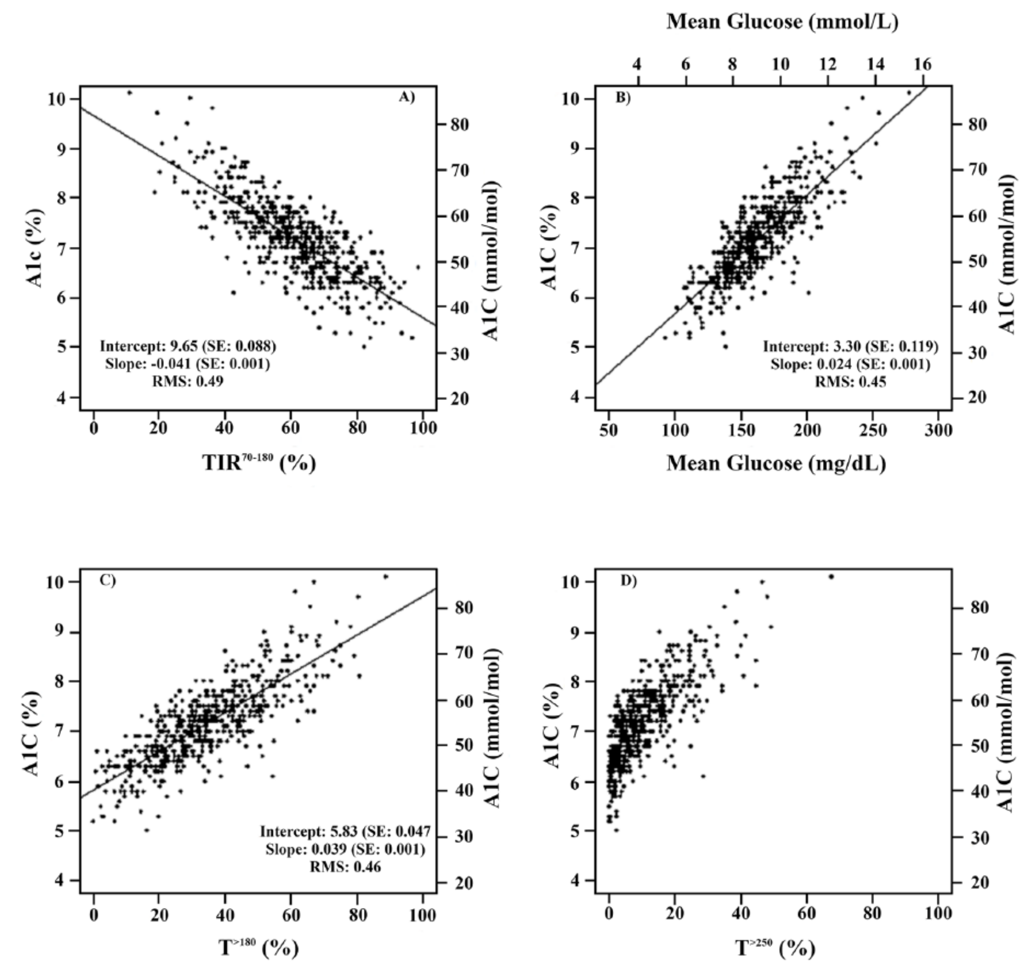

Figure 1. Scatter plots for selected CGM Metrics with A1C at month 6 (RMS = root mean square error) The Intercept, slope and RMS are not shown for A1C (%) vs $T>^{250}$ (%) in view of apparent nonlinearity of this relationship.

Table 4. Relationship of TIR and T > 180 to A1C.[a]

A. Estimation of A1C for a given TIR Level of CGM metric

	Baseline (N = 455)			Month 6 (N = 545)		
	Estimate	95% CI for the predicted value[b]	95% CI for the mean[b]	Estimate	95% CI for the predicted value[b]	95% CI for the mean[b]
			Estimated A1C (%)			
TIR^{70-180}						
20%	9.4	(8.0, 10.7)	(9.2, 9.5)	8.8	(7.9, 9.8)	(8.7, 9.0)
30%	8.9	(7.6, 10.2)	(8.7, 9.0)	8.4	(7.5, 9.4)	(8.3, 8.5)
40%	8.4	(7.1, 9.7)	(8.3, 8.5)	8.0	(7.1, 9.0)	(8.0, 8.1)
50%	7.9	(6.6, 9.2)	(7.9, 8.0)	7.6	(6.7, 8.6)	(7.6, 7.7)
60%	7.4	(6.1, 8.8)	(7.4, 7.5)	7.2	(6.3, 8.2)	(7.2, 7.3)
70%	7.0	(5.6, 8.3)	(6.9, 7.0)	6.8	(5.8, 7.8)	(6.8, 6.9)
80%	6.5	(5.2, 7.8)	(6.4, 6.6)	6.4	(5.4, 7.4)	(6.3, 6.5)
90%	6.0	(4.7, 7.3)	(5.9, 6.2)	6.0	(5.0, 7.0)	(5.9, 6.1)
Equation		$A1C = 10.31 - 0.048 \times TIR^{70-180}$			$A1C = 9.65 - 0.041 \times TIR^{70-180}$	
RMS[c]		0.67			0.49	
TIR^{70-140}						
20%	8.4	(7.0, 9.8)	(8.3, 8.5)	8.0	(7.0, 9.0)	(7.9, 8.0)
30%	7.9	(6.5, 9.2)	(7.8, 7.9)	7.5	(6.6, 8.5)	(7.5, 7.6)
40%	7.4	(6.0, 8.7)	(7.3, 7.4)	7.1	(6.1, 8.1)	(7.1, 7.2)
50%	6.8	(5.5, 8.2)	(6.7, 6.9)	6.7	(5.7, 7.7)	(6.6, 6.7)
60%	6.3	(5.0, 7.7)	(6.2, 6.4)	6.3	(5.3, 7.2)	(6.2, 6.3)
70%	5.8	(4.4, 7.2)	(5.6, 6.0)	5.8	(4.9, 6.8)	(5.7, 5.9)
80%	5.3	(3.9, 6.7)	(5.1, 5.5)	5.4	(4.4, 6.4)	(5.3, 5.5)
90%	4.8	(3.4, 6.1)	(4.5, 5.0)	5.0	(4.0, 6.0)	(4.8, 5.1)
Equation		$A1C = 9.43 - 0.052 \times TIR^{70-140}$			$A1C = 8.83 - 0.043 \times TIR^{70-140}$	
RMS[c]		0.69			0.50	
$T>^{180}$						
80%	9.5	(8.1, 10.8)	(9.3, 9.6)	8.9	(8.0, 9.9)	(8.8, 9.1)
70%	9.0	(7.7, 10.3)	(8.9, 9.2)	8.6	(7.6, 9.5)	(8.5, 8.6)
60%	8.6	(7.3, 9.9)	(8.5, 8.7)	8.2	(7.2, 9.1)	(8.1, 8.2)
50%	8.1	(6.8, 9.4)	(8.0, 8.2)	7.8	(6.9, 8.7)	(7.7, 7.8)
40%	7.7	(6.4, 9.0)	(7.6, 7.7)	7.4	(6.5, 8.3)	(7.3, 7.4)
30%	7.2	(5.9, 8.5)	(7.2, 7.3)	7.0	(6.1, 7.9)	(7.0, 7.0)
20%	6.8	(5.5, 8.1)	(6.7, 6.9)	6.6	(5.7, 7.5)	(6.6, 6.7)
10%	6.3	(5.0, 7.6)	(6.2, 6.5)	6.2	(5.3, 7.1)	(6.1, 6.3)
Equation		$A1C = 5.88 - 0.045 \times T>^{180}$			$A1C = 5.83 - 0.039 \times T>^{180}$	
RMS[c]		0.67			0.46	

B. Estimation of TIR^{70-180}, TIR^{70-140}, and $T>^{180}$ for given A1C

	Baseline (N = 455)			Month 6 (N = 545)		
A1C	Estimate	95% CI for the predicted value	95% CI for the mean	Estimate	95% CI for the predicted value	95% CI for the mean
			Estimated TIR^{70-180} (%)			
6.0%	75	(55, 95)	(73, 77)	79	(60, 97)	(77, 80)
6.5%	70	(50, 90)	(68, 71)	71	(53, 90)	(70, 72)
7.0%	64	(44, 84)	(63, 65)	64	(45, 82)	(63, 65)
7.5%	59	(38, 79)	(58, 59)	56	(38, 75)	(55, 57)
8.0%	53	(33, 73)	(52, 54)	49	(30, 67)	(48, 50)
8.5%	47	(27, 68)	(46, 49)	41	(23, 60)	(40, 43)
9.0%	42	(22, 62)	(40, 44)	34	(15, 53)	(32, 36)
Equation		$TIR^{70-180} = 141 - 11.1 \times A1C$			$TIR^{70-180} = 168 - 14.9 \times A1C$	
RMS[c]		10.2			9.5	

(continued)

Table 4. (continued)

B. Estimation of $TIR^{70\text{-}180}$, $TIR^{70\text{-}140}$, and $T>^{180}$ for given A1C

	Baseline (N = 455)			Month 6 (N = 545)		
A1C	Estimate	95% CI for the predicted value	95% CI for the mean	Estimate	95% CI for the predicted value	95% CI for the mean
			Estimated $TIR^{70\text{-}140}$ (%)			
6.0%	51	(33, 70)	(50, 53)	55	(37, 73)	(54, 57)
6.5%	47	(28, 65)	(45, 48)	48	(30, 66)	(47, 49)
7.0%	42	(23, 60)	(41, 43)	41	(23, 59)	(40, 42)
7.5%	37	(18, 55)	(36, 38)	34	(16, 52)	(33, 35)
8.0%	32	(14, 51)	(31, 33)	27	(9, 45)	(26, 28)
8.5%	27	(9, 46)	(26, 28)	20	(2, 38)	(19, 22)
9.0%	22	(4, 41)	(21, 24)	13	(-5, 31)	(11, 15)
Equation	$TIR^{70\text{-}140} = 109 - 9.6\times A1C$			$TIR^{70\text{-}140} = 139 - 14.0\times A1C$		
RMS[c]	9.4			9.0		
			Estimated $T>^{180}$ (%)			
6.0%	19	(-3, 40)	(17, 20)	15	(-4, 34)	(14, 17)
6.5%	25	(3, 46)	(23, 26)	23	(4, 42)	(22, 24)
7.0%	30	(9, 52)	(29, 32)	32	(13, 51)	(31, 33)
7.5%	36	(15, 58)	(35, 37)	40	(21, 59)	(39, 41)
8.0%	42	(21, 64)	(41, 44)	48	(29, 67)	(47, 50)
8.5%	48	(27, 70)	(47, 50)	57	(38, 76)	(55, 58)
9.0%	54	(33, 76)	(53, 56)	65	(46, 84)	(63, 67)
Equation	$T>^{180} = -53 + 11.9\times A1C$			$T>^{180} = -85 + 16.7\times A1C$		
RMS[c]	10.9			9.6		

[a]Simple linear regression models were used to assess relationship between A1C and selected CGM metrics at baseline and month 6 separately.
[b]The 95% CI for the mean represents the range within which the true mean is likely to be, whereas the 95% CI for the predictive value represents the range within which the true value for an individual's value is likely to be.
[c]RMS = root mean square error from the least squares regression model.

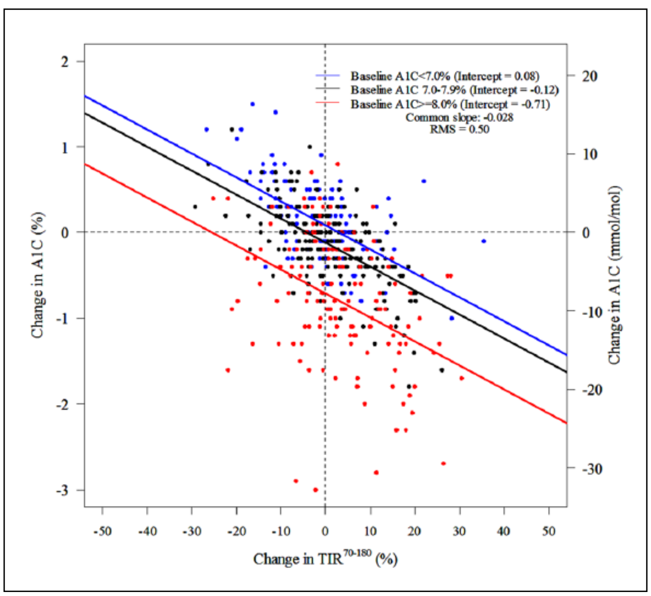

Figure 2. Scatter plots for change in $TIR^{70\text{-}180}$ versus change in A1C (slopes were constrained to be identical for all three subgroups for A1C at baseline; RMS = root mean square error).

Although the present authors propose to move beyond A1C and rely primarily on CGM for diabetes management decisions, we recognize that most clinicians and patients are not ready to do so. Thus, the estimate of A1C derived from CGM metrics will have clinical relevance as long as A1C targets are being used to direct approaches to diabetes management. Until recently, when it was removed at the suggestion of the US Food and Drug Administration (FDA), many displays of CGM data showed an estimated A1C calculated from mean glucose, usually based on the ADAG study.[3,4] To reduce confusion when the estimated A1C and measured A1C were discordant, it has been proposed to refer to this predicted value of A1C as the Glucose Management Indicator (GMI).[18] The authors of this publication developed the term GMI with input and collaboration from many in the diabetes community including members of the Center for Devices and Radiological Health (CDRH), a division of the FDA that regulates medical devices, including CGM systems.

The present study shows that a predicted (estimated) A1C based on $TIR^{70\text{-}180}$ or on $T>^{180}$ have essentially the same degree of precision and reliability as an estimated A1C based on mean glucose. For now, the estimated A1C based on mean

Table 5. Relationship of Change in TIR and T > 180 to Change in A1C According to Baseline A1C Level.[a]

	Overall (N = 455)		Baseline A1C <7.0% (n = 131)		Baseline A1C 7.0-7.9% (n = 182)		Baseline A1C ≥8.0% (n = 142)	
	Estimate	95% CI for the predicted value	Estimate	95% CI for the predicted value	Estimate	95% CI for the predicted value	Estimate	95% CI for the predicted value
A. Estimation of change in A1C for a given level of CGM metric[a]								
	Estimated Change in A1C from Baseline (%)							
Change in TIR^{70-180}								
−20%	+0.42	(−0.76, +1.60)	+0.64	(−0.35, +1.64)	+0.45	(−0.55, +1.44)	−0.14	(−1.14, +0.85)
−15%	+0.25	(−0.92, +1.43)	+0.50	(−0.49, +1.50)	+0.31	(−0.69, +1.30)	−0.29	(−1.28, +0.71)
−10%	+0.09	(−1.08, +1.26)	+0.36	(−0.63, +1.35)	+0.16	(−0.83, +1.16)	−0.43	(−1.42, +0.57)
−5%	−0.08	(−1.25, +1.10)	+0.22	(−0.77, +1.21)	+0.02	(−0.97, +1.01)	−0.57	(−1.56, +0.42)
0%	−0.24	(v1.41, +0.93)	+0.08	(−0.91, +1.07)	−0.12	(−1.11, +0.87)	−0.71	(−1.70, +0.28)
+5%	−0.41	(−1.58, +0.76)	−0.06	(−1.06, +0.93)	−0.26	(−1.25, +0.73)	−0.85	(−1.84, +0.14)
+10%	−0.57	(−1.74, +0.60)	−0.21	(−1.20, +0.79)	−0.40	(−1.39, +0.59)	−0.99	(−1.99, −0.00)
+15%	−0.74	(−1.91, +0.43)	−0.35	(−1.34, +0.65)	−0.54	(−1.54, +0.45)	−1.14	(−2.13, −0.14)
+20%	−0.90	(−2.08, +0.27)	−0.49	(−1.49, +0.51)	−0.69	(−1.68, +0.31)	−1.28	(−2.27, −0.28)
Equation: ΔA1C =	$-0.24 - 0.033 \times \Delta TIR^{70-180}$		$0.08 - 0.028 \times \Delta TIR^{70-180}$		$-0.12 - 0.028 \times \Delta TIR^{70-180}$		$-0.71 - 0.028 \times \Delta TIR^{70-180}$	
RMS[b]		0.59				0.50		
Change in TIR^{70-140}								
−20%	+0.40	(−0.79, +1.59)	+0.64	(−0.37, +1.64)	+0.45	(−0.55, +1.45)	−0.16	(−1.17, +0.84)
−15%	+0.23	(−0.95, +1.42)	+0.49	(−0.51, +1.49)	+0.31	(−0.69, +1.31)	−0.31	(−1.31, +0.69)
−10%	+0.07	(−1.12, +1.25)	+0.35	(−0.65, +1.34)	+0.16	(−0.84, +1.16)	−0.45	(−1.45, +0.55)
−5%	−0.10	(−1.28, +1.08)	+0.20	(−0.80, +1.20)	+0.02	(−0.98, +1.01)	−0.60	(−1.60, +0.40)
0%	−0.27	(−1.45, +0.92)	+0.06	(−0.94, +1.05)	−0.13	(−1.12, +0.87)	−0.74	(−1.74, +0.25)
+5%	−0.43	(−1.62, +0.75)	−0.09	(−1.09, +0.91)	−0.27	(−1.27, +0.72)	−0.89	(−1.89, +0.11)
+10%	−0.60	(−1.78, +0.59)	−0.23	(−1.23, +0.76)	−0.42	(−1.42, +0.58)	−1.03	(−2.03, −0.04)
+15%	−0.77	(−1.95, +0.42)	−0.38	(−1.38, +0.62)	−0.56	(−1.56, +0.44)	−1.18	(−2.18, −0.18)
+20%	−0.93	(−2.12, +0.26)	−0.53	(−1.53, +0.48)	−0.71	(−1.71, +0.29)	−1.32	(−2.33, −0.32)
Equation: ΔA1C =	$-0.27 - 0.033 \times \Delta TIR^{70-140}$		$0.06 - 0.029 \times \Delta TIR^{70-140}$		$-0.13 - 0.029 \times \Delta TIR^{70-140}$		$-0.74 - 0.029 \times \Delta TIR^{70-140}$	
RMS[b]		0.60				0.51		
Change in $T>^{180}$								
+20%	+0.32	(−0.86, +1.50)	+0.58	(−0.40, +1.56)	+0.39	(−0.59, +1.37)	−0.23	(−1.21, +0.76)
+15%	+0.17	(−1.00, +1.35)	+0.45	(−0.53, +1.43)	+0.26	(−0.72, +1.24)	−0.36	(−1.34, +0.63)
+10%	+0.03	(−1.15, +1.20)	+0.32	(−0.66, +1.30)	+0.13	(−0.85, +1.11)	−0.49	(−1.47, +0.49)
+5%	−0.12	(−1.30, +1.05)	+0.19	(−0.79, +1.17)	−0.00	(−0.98, +0.98)	−0.62	(−1.60, +0.36)
0%	−0.27	(−1.44, +0.90)	+0.06	(−0.92, +1.04)	−0.13	(−1.11, +0.85)	−0.75	(−1.73, +0.23)
−5%	−0.42	(−1.59, +0.76)	−0.07	(−1.06, +0.91)	−0.26	(−1.24, +0.72)	−0.88	(−1.86, +0.10)
−10%	−0.56	(−1.74, +0.61)	−0.21	(−1.19, +0.78)	−0.39	(−1.38, +0.59)	−1.01	(−1.99, −0.03)
−15%	−0.71	(−1.89, +0.46)	−0.34	(−1.32, +0.65)	−0.53	(−1.51, +0.46)	−1.14	(−2.12, −0.16)
−20%	−0.86	(−2.04, +0.32)	−0.47	(−1.45, +0.52)	−0.66	(−1.64, +0.33)	−1.27	(−2.26, −0.29)
Equation: ΔA1C =	$-0.27 + 0.029 \times \Delta T>^{180}$		$0.06 + 0.026 \times \Delta T>^{180}$		$-0.13 + 0.026 \times \Delta T>^{180}$		$-0.75 + 0.026 \times \Delta T>^{180}$	
RMS[b]		0.60				0.50		
B. Estimation of change in TIR^{70-180}, TIR^{70-140}, and $T>^{180}$ for a given change in A1C								
Change in A1C	Estimated change in TIR^{70-180} from baseline (%)							
−2.0%	+13.5	(−3.9, +30.9)	+19.6	(+3.2, +36.0)	+24.9	(+9.5, +40.4)	+10.0	(−10.6, +30.7)
−1.5%	+9.9	(−7.4, +27.2)	+14.7	(−1.2, +30.7)	+18.5	(+3.3, +33.6)	+7.1	(−13.4, +27.7)
−1.0%	+6.3	(−11.0, +23.6)	+9.8	(−5.8, +25.4)	+12.0	(−2.9, +26.9)	+4.2	(−16.2, +24.7)
−0.5%	+2.7	(−14.6, +20.0)	+5.0	(−10.4, +20.4)	+5.5	(−9.3, +20.4)	+1.3	(−19.2, +21.8)
0%	−0.9	(−18.2, +16.4)	+0.1	(−15.2, +15.4)	−0.9	(−15.7, +13.9)	−1.6	(−22.1, +19.0)
+0.5%	−4.5	(−21.8, +12.8)	−4.8	(−20.1, +10.5)	−7.4	(−22.3, +7.5)	−4.5	(−25.2, +16.2)
+1.0%	−8.1	(−25.5, +9.2)	−9.7	(−25.2, +5.8)	−13.9	(−28.9, +1.2)	−7.4	(−28.2, +13.5)
Equation: ΔTIR^{70-180} =	$-0.92 - 7.21 \times \Delta A1C$		$0.09 - 9.75 \times \Delta A1C$		$-0.93 - 12.93 \times \Delta A1C$		$-1.56 - 5.80 \times \Delta A1C$	
RMS[b]		8.8		7.7		7.5		10.3

(continued)

Table 5. (continued)

	Overall (N = 455)		Baseline A1C <7.0% (n = 131)		Baseline A1C 7.0-7.9% (n = 182)		Baseline A1C ≥8.0% (n = 142)	
	Estimate	95% CI for the predicted value	Estimate	95% CI for the predicted value	Estimate	95% CI for the predicted value	Estimate	95% CI for the predicted value
Change in A1C	Estimated change in TIR^{70-140} from baseline (%)							
−2.0%	+11.8	(−5.0, +28.7)	+23.4	(+6.4, +40.5)	+23.3	(+7.4, +39.2)	+7.2	(−10.1, +24.6)
−1.5%	+8.5	(−8.3, +25.3)	+17.5	(+0.9, +34.0)	+17.2	(+1.6, +32.8)	+5.0	(−12.2, +22.3)
−1.0%	+5.2	(−11.6, +21.9)	+11.5	(−4.7, +27.7)	+11.1	(−4.4, +26.5)	+2.8	(−14.4, +20.0)
−0.5%	+1.8	(−14.9, +18.6)	+5.5	(−10.4, +21.5)	+4.9	(−10.4, +20.2)	+0.5	(−16.7, +17.8)
0%	−1.5	(−18.2, +15.2)	−0.4	(−16.3, +15.5)	−1.2	(−16.5, +14.1)	−1.7	(−19.0, +15.6)
+0.5%	−4.8	(−21.6, +11.9)	−6.4	(−22.3, +9.5)	−7.3	(−22.7, +8.0)	−3.9	(−21.3, +13.4)
+1.0%	−8.2	(−24.9, +8.6)	−12.3	(−28.4, +3.8)	−13.4	(−28.9, +2.1)	−6.2	(−23.7, +11.4)
Equation: ΔTIR^{70-140} =	−1.50 − 6.66×ΔA1C		−0.42 − 11.9×ΔA1C		−1.19 − 12.2×ΔA1C		−1.70 − 4.47×ΔA1C	
RMS[b]	8.5		8.0		7.7		8.7	
Change in A1C	Estimated change in $T>^{180}$ from baseline (%)							
+1.0%	+10.0	(−9.4, +29.4)	+14.4	(−0.8, +29.7)	+15.6	(−1.4, +32.5)	+9.4	(−14.4, +33.1)
+0.5%	+6.0	(−13.4, +25.3)	+7.4	(−7.7, +22.5)	+8.6	(−8.2, +25.3)	+6.3	(−17.3, +29.8)
0%	+2.0	(−17.4, +21.3)	+0.3	(−14.7, +15.4)	+1.5	(−15.1, +18.2)	+3.1	(−20.2, +26.5)
−0.5%	−2.0	(−21.4, +17.3)	−6.7	(−21.9, +8.4)	−5.5	(−22.2, +11.2)	+0.0	(−23.3, +23.3)
−1.0%	−6.0	(−25.4, +13.3)	−13.8	(−29.2, +1.6)	−12.5	(−29.3, +4.3)	−3.1	(−26.4, +20.2)
−1.5%	−10.0	(−29.4, +9.4)	−20.8	(−36.6, −5.1)	−19.5	(−36.6, −2.4)	−6.2	(−29.5, +17.2)
−2.0%	−14.0	(−33.5, +5.4)	−27.9	(−44.1, −11.7)	−26.5	(−43.9, −9.1)	−9.3	(−32.8, +14.2)
Equation: $\Delta T>^{180}$ =	1.97 + 8.00×ΔA1C		0.33 + 14.11×ΔA1C		1.55 + 14.04×ΔA1C		3.14 + 6.22×ΔA1C	
RMS[b]	9.8		7.6		8.4		11.7	

[a]Simple linear regression models were used to assess the relationship between change in A1C and change in selected CGM metrics for the entire cohort. For the subgroup analyses by baseline A1C, in part A, slopes were forced to be the same across subgroups since there were no significant interaction between baseline A1C and all 3 predictors; in part B, regression models were done separately in each subgroup since there were significant interactions between baseline A1C and change in A1C.
[b]RMS = root mean square error from the least squares regression model.

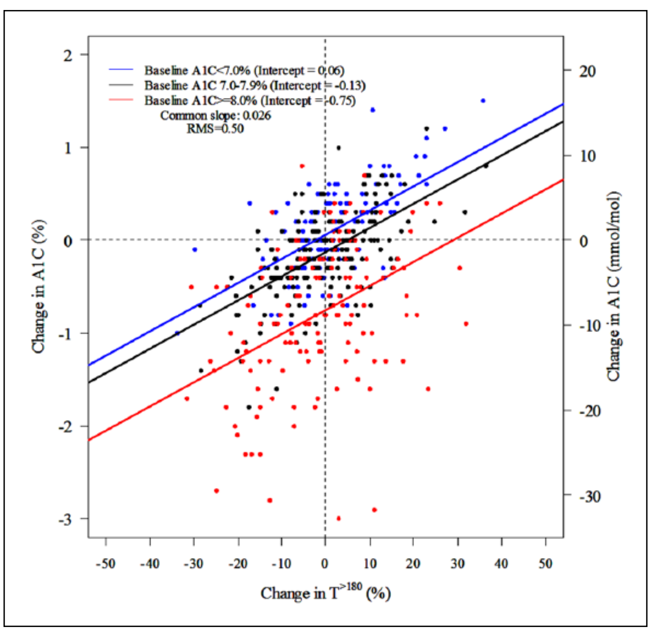

Figure 3. Scatter plots for change in $T>^{180}$ versus change in A1C (slopes were constrained to be identical for all three subgroups for A1C at baseline; RMS = root mean square error).

glucose (calculating a GMI) is the standard. In the future, it will be essential to indicate exactly how the estimated A1C was calculated. Although there may be utility in estimating A1C from CGM metrics, the estimation of TIR, mean glucose and hyperglycemia metrics from A1C would appear to have limited clinical relevance since the actual values will be available if CGM is being used as the basis for diabetes management. Although an observed laboratory A1C value of 8.0% on average corresponds to an estimated TIR^{70-180} of about 50% and a laboratory-measured A1C of 7.0% corresponds to an estimated TIR^{70-180} of about 64%, the conversion of a laboratory A1C to an expected TIR^{70-180} is not necessary or particularly useful for diabetes management.

The results comparing change in TIR^{70-180} versus change in A1C also demonstrate a wide degree of interindividual variability. For a given change in TIR^{70-180}, even for no change in TIR^{70-180}, there is a large spread in the observed change in A1C. This finding was similar for change in $T>^{180}$ versus change in A1C so the discordance between change in TIR^{70-180} and change in A1C isn't due to the impact of hypoglycemia on TIR^{70-180}. Roughly an increase in TIR^{70-180} or a decrease in $T>^{180}$ of 10% (corresponding to 2.4 hours per day) is associated with a reduction in A1C of about 0.6%.

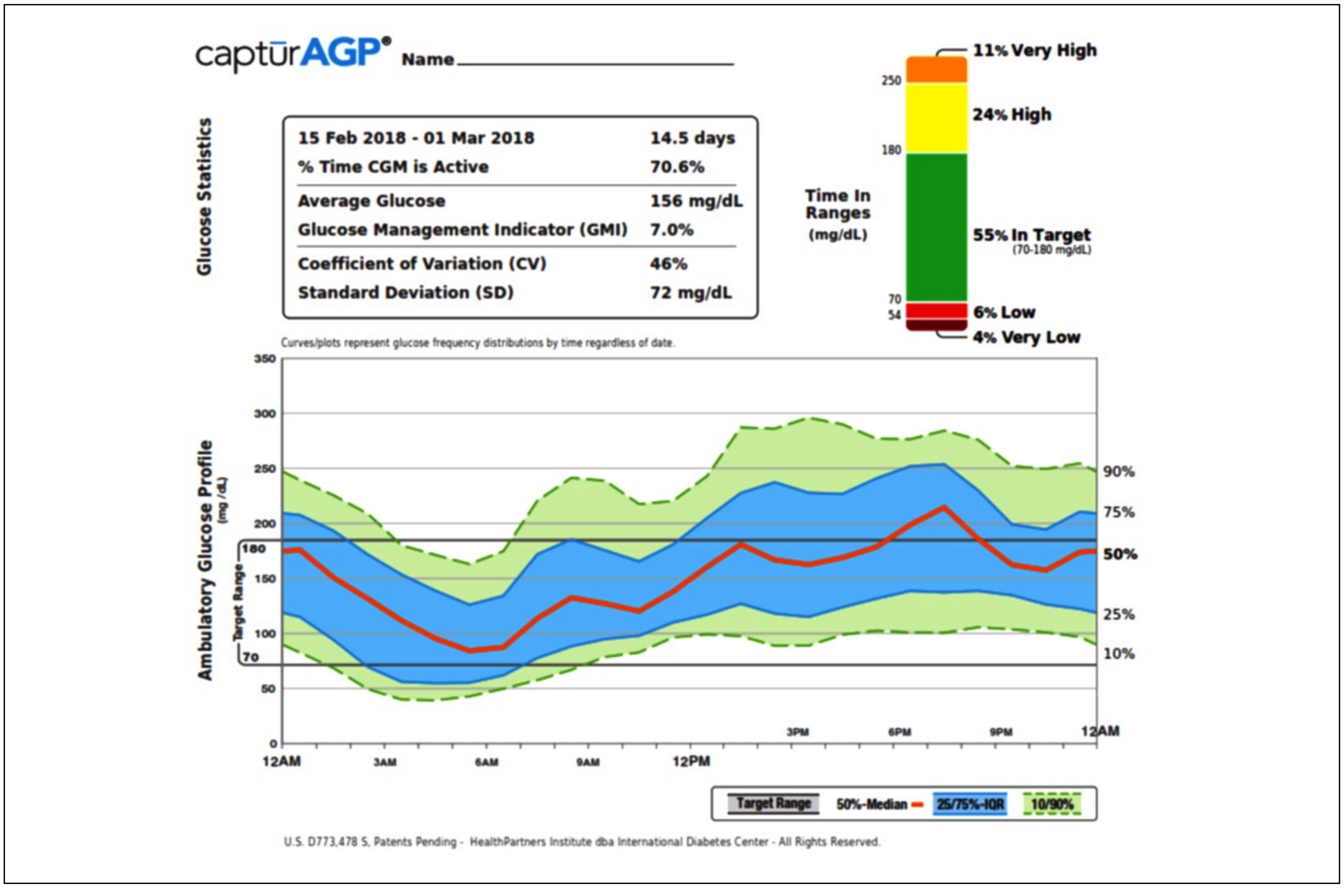

Figure 4. Example of ambulatory glucose profile (AGP). The AGP shows glucose patterns over time, which provides considerable information for optimizing diabetes management by identifying specific times of day with hyperglycemia or hypoglycemia.[20-23] The inset shows time in ranges for five ranges (very low <54 mg/dL to very high >250 mg/dL).[20,24]

However, with baseline A1C ≥8.0%, for example, a 10% increase in TIR was associated on average with a change in A1C of approximately −1% whereas for subjects with a baseline A1C of 7.0-7.9%, a 10% increase in TIR was associated on average with a change in A1C of only −0.4%.

For comparative purposes, it is useful to understand the distribution of CGM values in individuals without diabetes. In a recent study that included 96 adults (≥18 years old, A1c <5.7% and negative islet cell antibodies) without diabetes who wore a masked Dexcom G6 sensor for a median of 205 hours, median $TIR^{70\text{-}180}$ was 99% (IQR 97% to 99%), median $TIR^{70\text{-}140}$ was 95% (IQR 92% to 97%) and median mean glucose concentration was 99 mg/dL (IQR 95 to 105); 1% of participants had at least 2% glucose values >180 mg/dL, none had at least 1% >250 mg/dL, 35% had at least 2% <70 mg/dL, and 5% had at least 1% <54 mg/dL.[19] Although some of the out-of-range values may have been due to sensor errors (particularly for $T^{<54}$—possibly due to a compression artifact while sleeping), these data are useful for comparative purposes when evaluating CGM data from individuals with diabetes.

The main limitation of these analyses is that the data are reflective of a population of individuals who participated in clinical trials, which may not be representative of the full population of adults with T1D. A potential limitation is that the data from the JDRF CGM RCT were collected with older generation sensors. However, analyses excluding results from that study produced similar results. Another potential limitation is that the amount of baseline data was less than the amount in month 6, but a minimum of 10 days of baseline data were required for the baseline and change from baseline analyses since prior studies have shown that 10-14 days of CGM data generally are sufficient to approximate the results based on 3 months of data and for correlation with A1C.[20,21]

A rationale that has been championed for why A1C should remain the gold standard for assessing glycemic control is that A1C is the only metric that has been associated with chronic diabetic complications. However, recently Beck et al demonstrated using the Diabetes Control and Complications (DCCT) dataset that TIR and the other hyperglycemia metrics computed from 7-point blood glucose testing every 3 months were strongly associated with the risk of retinopathy and microalbuminuria.[20] A recent cross-sectional study of CGM metrics from individuals with type 2 diabetes demonstrated an association of time in range (TIR) with the presence of diabetic retinopathy.[22] Nevertheless, A1C remains a valuable metric for assessing glycemic control. It can be measured easily with precision and does not require the wearing of a device.

However, as CGM use becomes more widespread, the value of A1C may lessen with greater emphasis placed instead on $TIR^{70\text{-}180}$ as a metric of overall glucose control. $TIR^{70\text{-}180}$ is readily understandable by individuals with diabetes and in a survey it was recognized as an important indicator for diabetes management.[23,24] Since $TIR^{70\text{-}180}$ is an indirect measure of hyperglycemia with a very high negative correlation with $T{>}^{180}$ (Table 3, Figure S1a) as previously noted,[11] both $TIR^{70\text{-}180}$ and a metric of time in hypoglycemia (eg, $T{<}^{70}$ and $T{<}^{54}$) are needed to guide therapeutic decisions. Even what appears to be a small change in TIR can be clinically important: a 5% change in either $TIR^{70\text{-}180}$, $T{>}^{180}$, $T{<}^{70}$, or $T{<}^{54}$ represents 1.2 hours per day, while a 10% change represents 2.4 hours per day. As the medical community places greater reliance on CGM for diabetes management and less reliance on A1C, it will be important to establish targets for CGM metrics. The data reported herein are useful for this purpose. $TIR^{70\text{-}180}$ of 50% for instance corresponds on average to an A1C of close to 8%, but to achieve the ADA A1C target for adults of 7.0%, the equivalent $TIR^{70\text{-}180}$ target would be about 70%.

The information available from CGM to assist with diabetes management goes well beyond just the glycemic metrics that can be calculated. This information becomes evident in a display of glucose patterns versus time of day in a report such as the Ambulatory Glucose Profile (AGP, Figure 4). The AGP provides considerable information for optimizing diabetes management.[25-28] The "stacked bar chart" showing the percentages of time in multiple ranges, was introduced by Rodbard[29] and is part of the standardized AGP report.[25] Rodbard also has illustrated several graphical methods for use of TIRs that can be used to evaluate quality of glycemic control.[30] As use of CGM becomes more widespread, and as progressively more data become available confirming that TIR correlates with long-term diabetes complications,[20,22] we expect that we may reach a point in the future where A1C adds little to the wealth of information available from CGM to make diabetes management decisions.

Abbreviations

A1C, hemoglobin A1c; $AUC{>}^{180}$, area under the curve 180 mg/dL; CGM, continuous glucose monitoring; FDA, US Food and Drug Administration; GMI, Glucose Management Indicator; HBGI, high blood glucose index; IQR, interquartile range; JDRF CGM RCT, Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Randomized Clinical Trial; $T{<}^{54}$, time <54 mg/dL; $T{<}^{70}$, time < 70 mg/dL; $T{>}^{180}$, time >180 mg/dL; $T{>}^{250}$, time >250 mg/dL; $TIR^{70\text{-}140}$, time in range 70-140 mg/dL; $TIR^{70\text{-}180}$, time in range of 70-180 mg/dL.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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